

REMARKS**Amendments to the Claims**

Claims 11, 15, 18 and 21 have been canceled.

Claims 1, 3-5, 7-8 and 14 have been amended.

New Claim 22 has been added.

Claims 1, 3-5 and 7-8 have been amended to recite TNF α -mediated "neoplastic disease," and to delete reference to myelodysplastic syndrome. Support for these amendments can be found in the specification, for example, at page 3, lines 1-4 and page 59, lines 5 through 10. In addition, support is found in priority application 07/670,827, filed March 18, 1991, for example, at page 10, line 22 through page 11, line 9.

Claims 1 and 3-5 have been amended to recite "which comprises the variable region of monoclonal antibody A2 (ATCC Accession No. PTA-7045)." Support for these amendments is found in the specification, as amended, for example, at page 25, lines 16-23. In addition, support for reference to the cell line for the A2 antibody is found in the priority application US Serial No. 07/670,827, filed March 18, 1991, at page 19, lines 14-20.

Claims 1 and 5 have been amended to recite "antigen-binding fragment." Support is found in the specification, for example, at page 9, lines 8-11 and page 17, lines 2-8. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 1, lines 5-12 and page 11, lines 10-20.

Claim 1 has been further amended to recite "human constant region." Claim 5 has been amended to recite "human IgG1" constant region. Support is found in the specification, for example, at page 10, lines 8-15; page 31, line 6 to page 32, line 2; and page 34, lines 16-21. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 9, lines 21-23; page 12, lines 18-26; page 26, lines 6-19; and page 52, lines 18-20.

Claims 1 and 5 have been further amended to recite that the antibody or antigen-binding fragment "binds to a neutralizing epitope of human TNF α *in vivo* with an affinity of at least 1×10^8 liter/mole, measured as an association constant (K_a), as determined by Scatchard analysis." Support is found in the specification, for example, at page 21, lines 16-23; page 60, line 25 to

page 61, line 5; and Example X, particularly at page 80, line 24 to page 81, line 12. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 13, lines 5-8; page 18, lines 17-19; page 20, lines 3-6; and Example X, particularly, at page 67, line 12 to page 68, line 25.

Claim 14 has been amended to recite "the method of Claim 1 wherein said anti-TNF α antibody is a chimeric antibody." Support is found in the specification, for example, at page 10, lines 8-15 and page 17, lines 2-8. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 12, line 18 to page 13, line 4.

New Claim 22 recites "The antigen-binding fragment of Claim 1, wherein said fragment is selected from the group consisting of Fab, Fab', F(ab')₂ and Fv." Support is found in the specification, for example, at page 26, line 4. In addition, support is found in the specification of priority application US Serial No. 07/670,827, filed March 18, 1991, for example, at page 20, lines 16-19.

No new matter has been added by the amendments. Therefore, entry of the amendments into the application is respectfully requested.

Amendment to the Specification

Applicants have amended the title and abstract to recite neoplastic disease to be more descriptive of the claims as amended. Support for this amendment can be found in the specification, for example, at page 3, lines 1-4 and page 59, lines 5-10. In addition, support is found in priority application 07/670,827, filed March 18, 1991, at page 10, line 22 through page 11, line 9 and page 12, line 18 through page 13, line 4. This priority application is incorporated in the subject application by reference on page 1, lines 4-21.

In addition, Applicants have amended the paragraph at page 59, lines 5 through 10 to provide further antecedent basis for neoplastic disease (37 C.F.R. § 1.75(d) and M.P.E.P. § 608.01(l)). Support for this amendment can be found in the specification, for example, at page 3, lines 1-4 and page 59, lines 5 through 10.

Further, Applicants have amended the specification to correct the spelling of "Geysen" on page 86, line 26 to page 87, line 12. Applicants submit evidence that the correct spelling is "Geysen" in the enclosed Abstract (Exhibit A).

Lastly, Applicants have amended the specification to recite "ATCC Accession No. PTA-7045," and to recite that c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005. Support for this Amendment is found in the specification, for example, at page 25, lines 16-23.

No new matter has been added by these amendments. Therefore, entry of these amendments into the application is respectfully requested.

Priority

The Examiner states that neither the priority applications nor the instant application provides a sufficient description of a representative number of species to represent the entire genus of myelodysplastic syndrome, as currently claimed.

As discussed above, Claims 11, 15, 18 and 21 have been canceled. Claims 1, 3-5 and 7-8 have been amended to recite "TNF α -mediated neoplastic disease." Support for these amendments can be found in the specification, for example, at page 3, lines 1-4 and page 59, lines 5 through 10. In addition, support is found in priority application 07/670,827, filed March 18, 1991, for example, at page 10, line 22 through page 11, line 9 and page 12, line 18 through page 13, line 4.

Therefore, the priority application 07/670,827 (filed March 18, 1991) provides sufficient written description for Applicants' claimed methods of treating neoplastic disease, and Applicants are entitled to claim the benefit of it. This priority application has been properly referenced on page 1 of the specification in compliance with 35 U.S.C. § 120. Therefore, the priority of all pending claims is March 18, 1991.

Rejection of Claims 1, 3-5 and 7-21 Under 35 U.S.C. § 112, first paragraph

Claims 1, 3-5 and 7-21 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner states that the cA2 antibody must be known and readily available to the public, or obtainable by a repeatable method set forth in the specification, or else a deposit of the cell line/hybridoma may be made in order to satisfy the enablement requirement.

37 C.F.R. § 1.809 (b)(1) states that “[t]he applicant for patent or patent owner shall reply to the rejection under paragraph (a) of this section by (1) In the case of an applicant for patent, either making an acceptable original...deposit, or assuring the Office in writing that an acceptable deposit will be made....” In addition, 37 C.F.R. § 1.809 (d) states that “[f]or each deposit made pursuant to these regulations, the specification shall contain: (1) The accession number for the deposit; (2) The date of deposit; (3) A description of the deposited biological material sufficient to specifically identify it and to permit examination; and (4) The name and address of the depository.”

While Applicants disagree with the Examiner’s position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to expedite prosecution, and in accordance with 37 C.F.R. § 1.809 (b)(1), on September 22, 2005, Applicants deposited the cell line for the A2 antibody (designation c134A) with American Type Culture collection (ATCC) under the Budapest Treaty. The ATCC accession number is PTA-7045.

The specification at page 25, lines 16-23, has been amended to recite “As examples of antibodies according to the present invention, murine mAb A2 (ATCC Accession No. PTA-7045) of the present invention is produced by a cell line designated c134A.” The specification at page 25, lines 16-23 has been further amended to recite “c134A was deposited pursuant to the Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia 20110-2209, on September 22, 2005.”

Further, Claims 11, 15, 18 and 21 have been canceled. Claims 1 and 3-5 have been amended recite the ATCC accession number for the cell line of the A2 antibody. Dependent Claims 9-10, 12-13, 16-17, 19-20 and 22 depend from these claims and, therefore, contain the same limitation.

Filed concurrently herewith is a Statement Under 37 C.F.R. § 1.804, § 1.806 and § 1.808.

Thus, since Applicants have amended the specification and the claims to recite the ATCC Accession No. for the murine monoclonal antibody A2, the claims are enabled. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1, 3-5 and 7-21 Under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 1, 3-5 and 7-21 as indefinite in the recitation of “cA2”. Specifically, the Examiner states that “the use of ‘cA2’ antibody as the sole means of identifying the claimed antibody renders the claim indefinite because ‘cA2’ is merely a laboratory designation which does not clearly define the claimed product, since different laboratories may use the same laboratory designation [] to define completely distinct hybridomas / cell lines.”

While Applicants disagree with the Examiner’s position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claims 11, 15, 18 and 21 have been canceled. Claims 1 and 3-5 have been amended to recite the ATCC accession number for the cell line of the A2 antibody. Dependent Claims 12-14, 16, 17, 19, 20 and 22 depend from these claims and, therefore, contain the same limitation. As discussed above, on September 22, 2005, Applicants deposited the cell line for the A2 antibody with ATCC under the Budapest Treaty. The specification at page 25, lines 16-23 have been amended to recite the ATCC accession number, the date of deposit, a description of the biological material and the name and address of the depository. The Examiner has indicated that amending the claims to recite the appropriate ATCC Accession number would obviate this rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 11 and 14-15 Under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 11 and 14-15 as indefinite in the recitation of “neutralizing epitope of human TNF α .” The Examiner states that “Claims 11 and 14-15 are indefinite in the recitation of ‘neutralizing epitope of human TNF’”

While Applicants disagree with the Examiner’s position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as

discussed above, Claims 11 and 15 have been canceled, and Claim 14 has been amended, and, as amended, it no longer recites 'neutralizing epitope of human TNF'.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection to Claims 1, 3-5 and 7-21 Under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1, 3-5 and 7-21 as being unpatentable over Verhoef *et al.*, Leukemia, 6:1268-1272 (1992) in view of Le *et al.* (WO 92/16553). The Examiner states that "...it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teachings of Le *et al.* to those of Verhoef *et al.* to obtain antagonistic TNF- α -specific antibodies, including those with the cA2 specificity to counter the negative effects of TNF- α in myelodysplastic syndrome."

While Applicants disagree with the Examiner's position and reserve their rights to file continuing or divisional applications to pursue these claims, in order to further prosecution, as discussed above, Claims 11, 15, 18 and 21 have been canceled. Claims 1, 3-5 and 7-8 have been amended to recite TNF α -mediated "neoplastic disease", thereby rendering the rejection moot. As discussed above, support for these claim amendments is found in the specification, for example, at page 3, lines 1-4 and page 59, lines 5-10. In addition, support is found in priority application 07/670,827, filed March 18, 1991, at page 10, line 22 through page 11, line 9 and page 12, line 18 through page 13, line 4. Therefore, neither Le *et al.* (filed March 18, 1992 and published October 1, 1992) nor Verhoef *et al.* (1992) are prior art. Thus, the claims, as amended, are entitled to priority to 07/670,827 (filed March 18, 1991). Thus, reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

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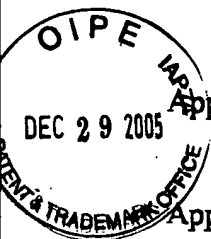
Concord, MA 01742-9133

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Attorney's Docket No.:0975.1005-014

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicants: Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David Knight and
Scott Siegel

Application No.: 10/010,229 Group: 1644

Filed: December 7, 2001 Examiner: Phillip Gambel

Confirmation No.: 8474

For: METHODS OF TREATING MYELODYSPLASTIC SYNDROME WITH ANTI-TNF
ANTIBODIES

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STATEMENT UNDER 37 C.F.R. §1.804, §1.806 AND §1.808

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Pursuant to 37 C.F.R. §1.804, §1.806 and §1.808, the undersigned states as follows:

1. Murine mAb A2 (c134A) was deposited on September 22, 2005, and assigned ATCC Accession Number PTA-7045. The above-referenced application specifically identifies this biological deposit, which was deposited under the Budapest Treaty at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209. I am a person in position to corroborate that the biological material which was deposited is a biological material

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specifically identified in the priority application U.S. Serial No. 07/670,827, filed March 18, 1991 (the filing date of which is relied upon) as filed.

2. Deposit PTA-7045 will be maintained in a public depository for the enforceable life of the patent which issues from the above-referenced application, a term of at least thirty years from the date of deposit or at least five years after the most recent request for the furnishing of a sample of the deposit is received by the depository, whichever is longer.
3. In accordance with 37 C.F.R. §1.808(a)(1), access to deposit PTA-7045 will be available during the pendency of the above-referenced application to one determined by the Commissioner to be entitled thereto under 37 C.F.R. §1.14 and 35 U.S.C. §122.
4. In accordance with 37 C.F.R. §1.808(a)(2), and except as permitted by 37 C.F.R. §1.808(b), all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent on the above-referenced application.

Respectfully submitted,

By



G. Kevin Townsend

Dated:

4/28/05



Peptides

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EXHIBIT

A synthetic strategy for epitope mapping

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Introduction

Synthetic peptides are attractive as probes for studying aspects of immunology at the molecular level, as possible diagnostic reagents, as characterized vaccine components and as hormone analogs. With the need for larger numbers of peptides for evaluation, fully automated synthesizers are widely used, and several methods have been described for the simultaneous synthesis of many peptides [1].

We describe a procedure allowing several thousand peptides to be concurrently synthesized at the rate of one residue coupled per day. With no practical restriction on the number of peptides which can be synthesized, a completely systematic approach to the location of epitopes (scan; Fig. 1) and their further resolution (replacement set; Fig. 2) becomes possible [2]. Good agreement has been shown between the results obtained from these rod-synthesized peptides and those from conventionally synthesized and purified peptides [3]. The stability of the rod-synthesized peptides on repeat testing allows their reuse for 30-60 tests.

This method has created the opportunity to address questions, which were formerly thought to be too difficult to answer, about the location of epitopes and their specificity for antibody.

Synthesis of Peptides

The method of peptide synthesis on rods has been described in detail elsewhere [2]. Briefly, specially-molded high-density polyethylene rods (diameter 4 mm) were suspended in deaerated 6% (v/v) acrylic acid in water containing 0.005 M CuSO_4 . Gamma-irradiation at a dose of 0.8 Mrad was used to graft polymerize the monomer to the rods as polyacrylic acid. After a wash cycle, dried grafted rods were assembled into specially molded polyethylene holders designed to hold 96 rods in the format and spacing of a microtiter plate. Subsequent reactions at the tips of the rods were carried out in the wells of a specially molded polyethylene tray.

An amino group was introduced by reacting the polyacrylic acid on the rods for 2-3 days with mono-(Boc)-1,6-diaminohexane in DMF using DCC to achieve the condensation. Following a conventional Boc-deprotection cycle with TFA

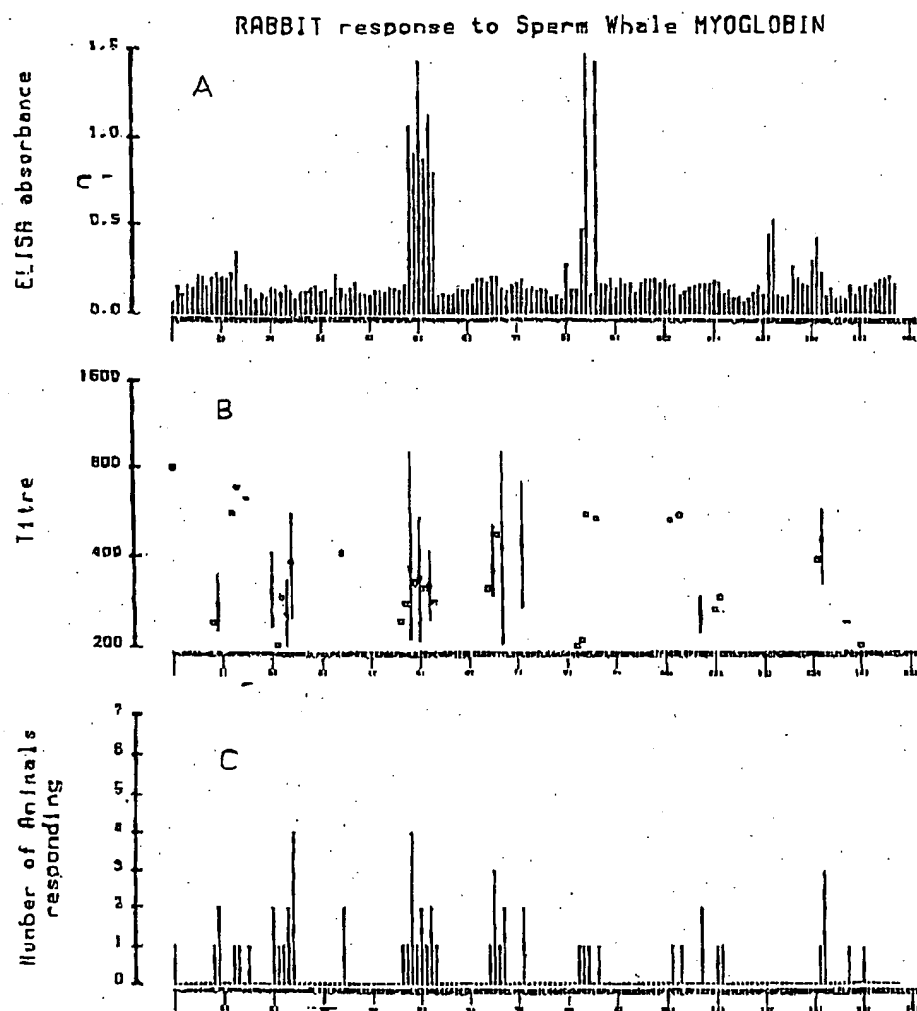


Fig. 1. Profiles of antigenic response (A-C) as a function of all possible sperm whale myoglobin (SWMb) hexapeptides. Each parameter is plotted as the sequence number corresponding to the first residue (amino-terminal) of the relevant hexapeptide. (A) Scan obtained from an individual rabbit anti-SWMb serum, used at a dilution of 1/400. The vertical axis shows the absorbance obtained at the end of the ELISA. (B) The individual titer (square) or, where more than one serum reacted, the geometric mean titer (circle) and the range of titers (vertical bar) of the antisera. Titers less than 200 (twice the slope of the test background) were ignored. (C) The frequency of the antigenic response given by the number of rabbit antisera that react with each hexapeptide.

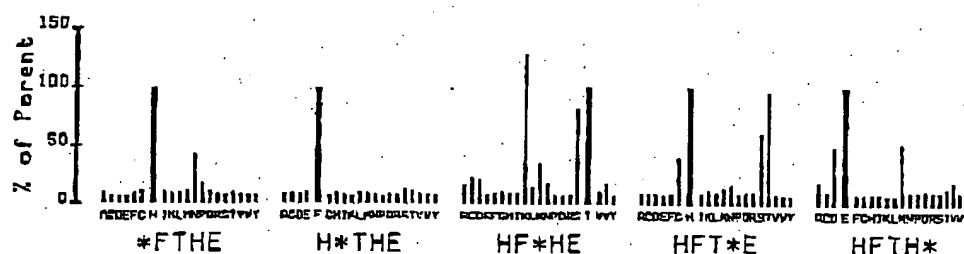


Fig. 2. Replacement set analysis, based on parent pentapeptide ⁵⁴HF*THE⁵⁸ homologous with myohemerythrin. Each block of 20 ELISA values represents the results with peptides containing the single amino acid substitution identified by the single letter code beneath each bar. The position of the substitution is indicated by an asterisk in the sequence given under that block. The homologous amino acid is emphasized. ELISA values for the five copies of the parent sequence have been averaged and taken as 100% for the purposes of comparison with replacement analogs. Dilution of rabbit antiserum used was 1/1000.

Boc- β -alanine was coupled for a limited time to a target density of 50 ± 10 nmol per rod tip. Unreacted amino groups were acetylated by reaction with acetic anhydride in DMF/TEA. Successive DCC/HOBT-mediated coupling reactions were carried out overnight using side-chain protected amino acids as dictated by the sequence to be synthesized. A microcomputer program was used to calculate the requirements for the preparation of the activated amino acid solutions, and to direct the addition of the correct amino acid to each rod on each day. At the completion of the final coupling reaction, and after removal of the Boc group, the terminal amino group was acetylated. Side-chain deprotection was achieved by reaction with 50 mM boron tris(trifluoroacetate) in dry TFA [4].

Detection of Binding of Antibody by the Rod-Coupled Peptides

ELISA reactions were carried out with the appropriate serum and conjugate solutions in polystyrene microtiter trays [1]. Briefly, the tips of the rods, with the peptides still attached, were precoated using a 2% protein solution to block nonspecific adsorption of antibodies. Rods were incubated overnight in an appropriate dilution of an antiserum, washed 4 times, and incubated for 1 h in 'conjugate', comprising horseradish peroxidase-labeled goat anti-Ig, specific for the antibody species under test.

After washing to remove unbound conjugate, the level of bound conjugate was determined by the color developed by the reaction with a solution of the enzyme substrate, hydrogen peroxide in phosphate/citrate buffer, pH 4.0.

containing ABTS. Bound antibody was removed from the rods prior to retesting with another antiserum.

Rationale of Strategy

The procedure for the synthesis of peptides as described was conceived in order to provide the very large numbers of peptides required for systematic screening for sequences with biological activity. As such, the following factors were considered:

(1) By ELISA, the detection of binding of antibody only requires peptide to be present in the range of picomol [5]. This condition is satisfied by the level of peptide produced on the tips of the rods, which is typically 30–50 nmol. Furthermore, we have observed comparable test absorbances for peptide densities varying over two orders of magnitude, indicating that the test is only limited by the concentration of antibody.

(2) As in the case with the majority of serological tests, where a given antigen is determined in the presence of a large excess of extraneous protein, absolute purity of a peptide is also not a necessary requirement. The specificity of the antibody is relied upon to distinguish between the nominal sequence synthesized and the inevitable small amounts of deletion sequences, termination peptides, or other byproducts formed during the synthesis.

(3) Large numbers of 'negative control sequences' are a natural consequence of the systematic way in which peptide sets are structured. As is the usual case, peptide sets consist of closely related sequences differing by only one or two amino acids from each other. The observation of antibody binding to one peptide but failing to bind to a closely related peptide is taken as good evidence for the specificity of the test.

Stability on Repeat Testing

As a consequence of the synthesis strategy in which completed peptide remains covalently coupled to the plastic support, reuse of peptide through a number of tests only requires removal of reacting antibody between tests. When the absolute value of the absorbance is monitored over many successive tests with the same peptides, a gradual decrease is observed. Experience with many sets of peptides suggests that 30–60 useful tests can be expected before it becomes necessary to resynthesize a particular set of peptides. Peptides have been stored (dry at 4°C) for extended periods between tests, without detectable loss of activity.

Discussion

The possibility that synthetic peptides may find uses as vaccines, diagnostics

and other biologically relevant agents has focused interest on methods which provide for large numbers of peptides for evaluation. It is our experience that using the methods described, a small laboratory could readily prepare more than 1000 peptides per month. Furthermore, the format of these peptides makes them ideally suited for repeated evaluation, and utilizes the same instrumentation as is routinely used for immunological testing. Identification of a peptide(s) with the desired properties can then be followed by the preparation of larger and well-characterized qualities, using well-established solid phase synthesis procedures.

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